UNIVERSITY OF COLORADO
CANCER CENTER

Proffered session: oral presentations HNSCC

Antonio Jimeno M.D., Ph.D.
Associate Professor of Oncology and Otolaryngology
Director, Head and Neck Cancer Medical Oncology Program
Director, Cancer stem cell-directed Clinical Trials Program

University of Colorado Cancer Center
Charles C. Gates Center for Stem Cell Biology

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Disclosures

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  - Vora family.
  - Mordecai Foundation.
  - Onconova Therapeutics.
  - Infinity.
  - Oncothyreon.

DISCUSSION

1. A Phase 2, Randomized Trial (CONCERT-2) of Panitumumab Plus Radiotherapy Compared With Chemoradiotherapy in Patients With Unresected, Locally Advanced Squamous Cell Carcinoma of the Head and Neck

2. Safety and Efficacy of Cisplatin plus 5-FU and Cetuximab in HPV-positive and HPV-negative Recurrent and/or Metastatic R/M SCCHN: Analysis of the Phase III EXTREME Trial

3. Preclinical Rational, Safety, and Preliminary Efficacy Results of Weekly Everolimus, Carboplatin and Paclitaxel as an induction Therapy for Patients with Unresectable Locally Advanced HNSCC

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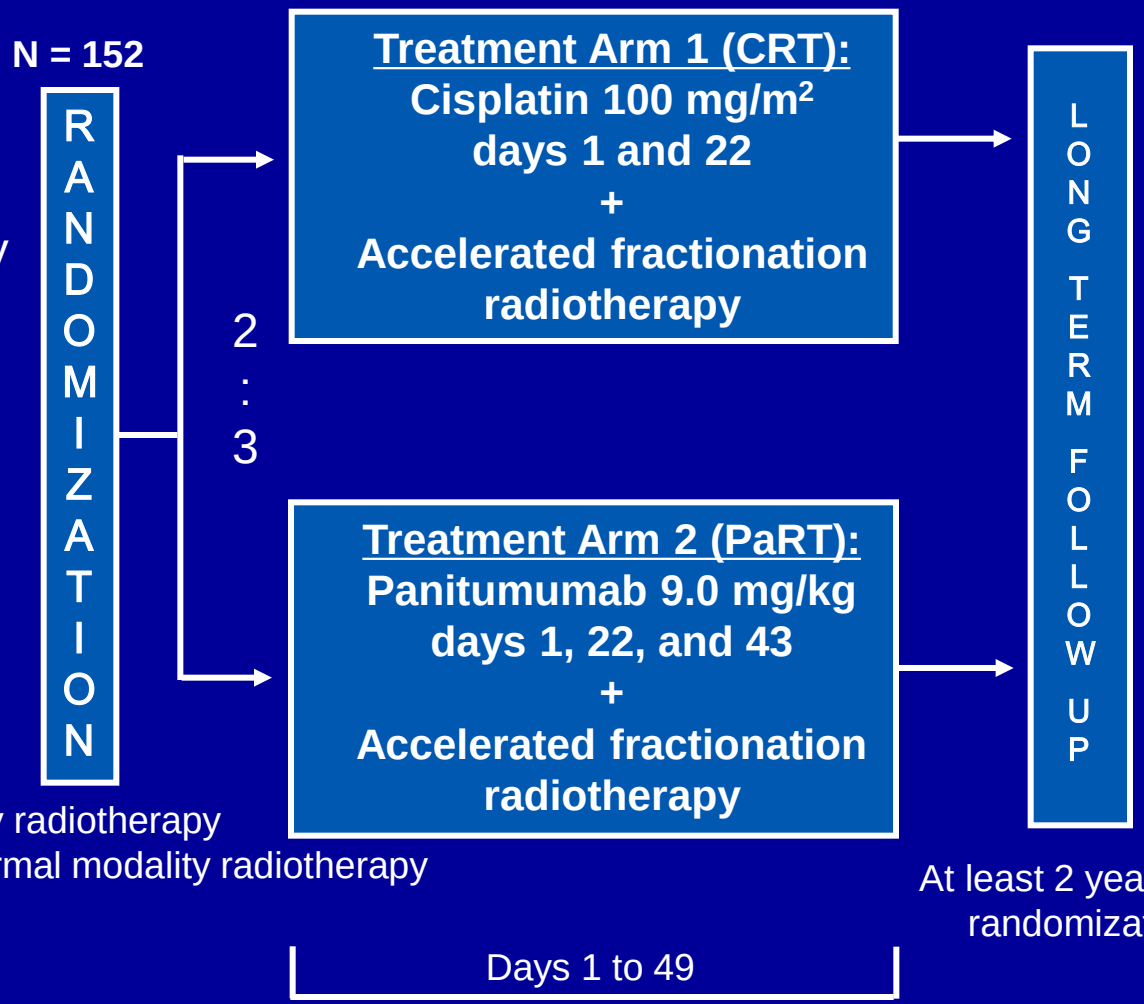
CONCERT-2 Panitumumab Plus Radiotherapy Compared With CRT in Patients With Unresected, Locally Advanced SCCHN

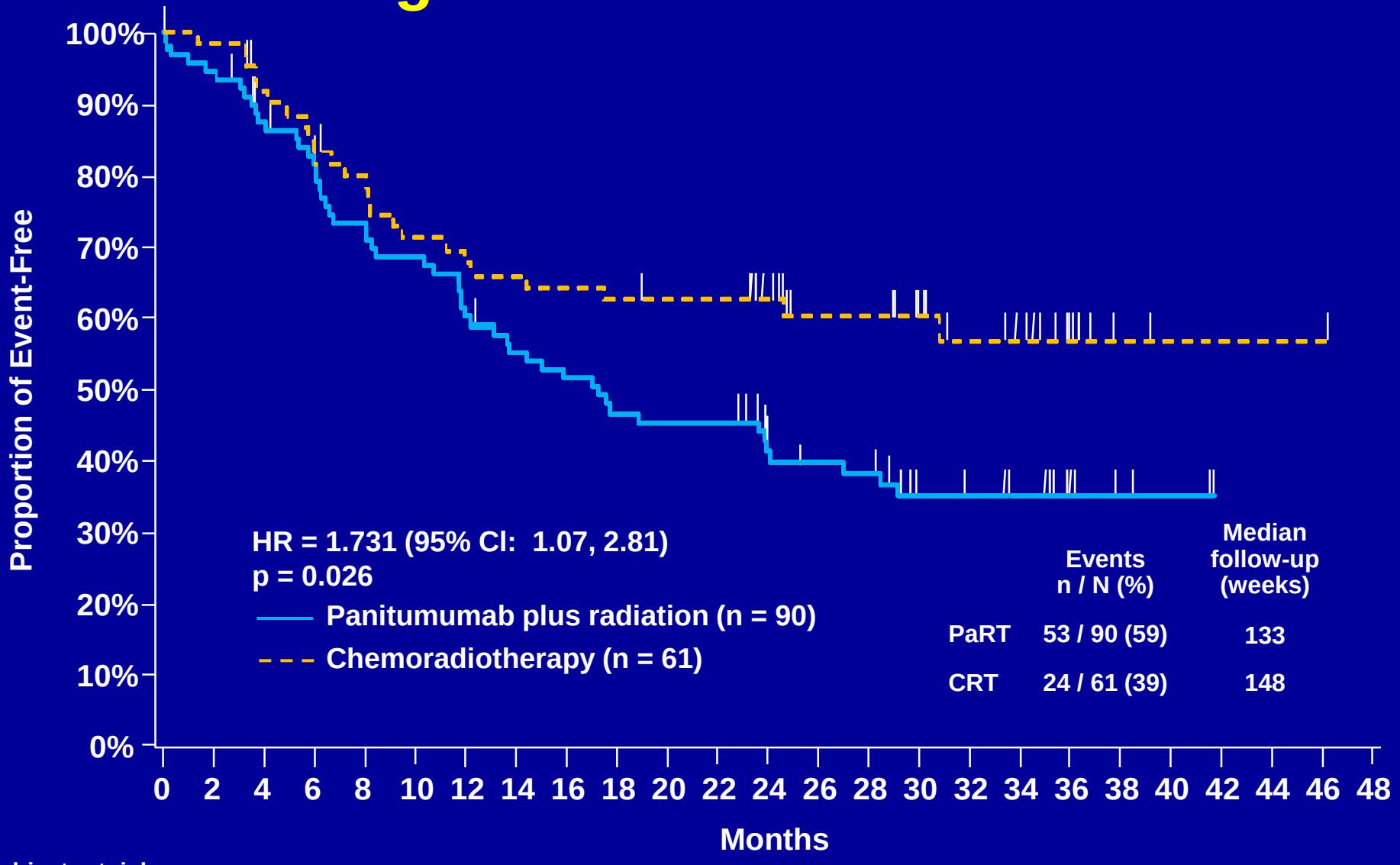
Stratification factors:

- Site of primary tumor: hypopharynx / oral cavity vs oropharynx / larynx
- RT delivery modality: IMRT* vs 3D-CRT**
- Nodal status: N0 vs N+
- Tumor stage: T1-3 vs T4



*IMRT = intensity-modulated modality radiotherapy
**3D-CRT = three-dimensional conformal modality radiotherapy

Progression-free Survival



Subjects at risk:

PRT	90	84	75	69	61	57	50	45	42	38	37	37	28	26	25	16	15	13	6	3	2	0	0	0	0
CRT	61	60	54	49	46	41	39	38	37	36	35	35	30	24	24	20	16	14	8	2	1	1	1	1	0

CONCLUSIONS

- Authors should be commended for attempting to address a very relevant question
- Even in a relatively small trial, there seemed to be a trend in favor of the CRT arm compared with the PaRT arm for LRC and OS, and PFS reached statistical significance
- Toxicity severity was similar in both arms
  - Crucial finding, particularly for the shared, RT-related mucositis and odynophagia

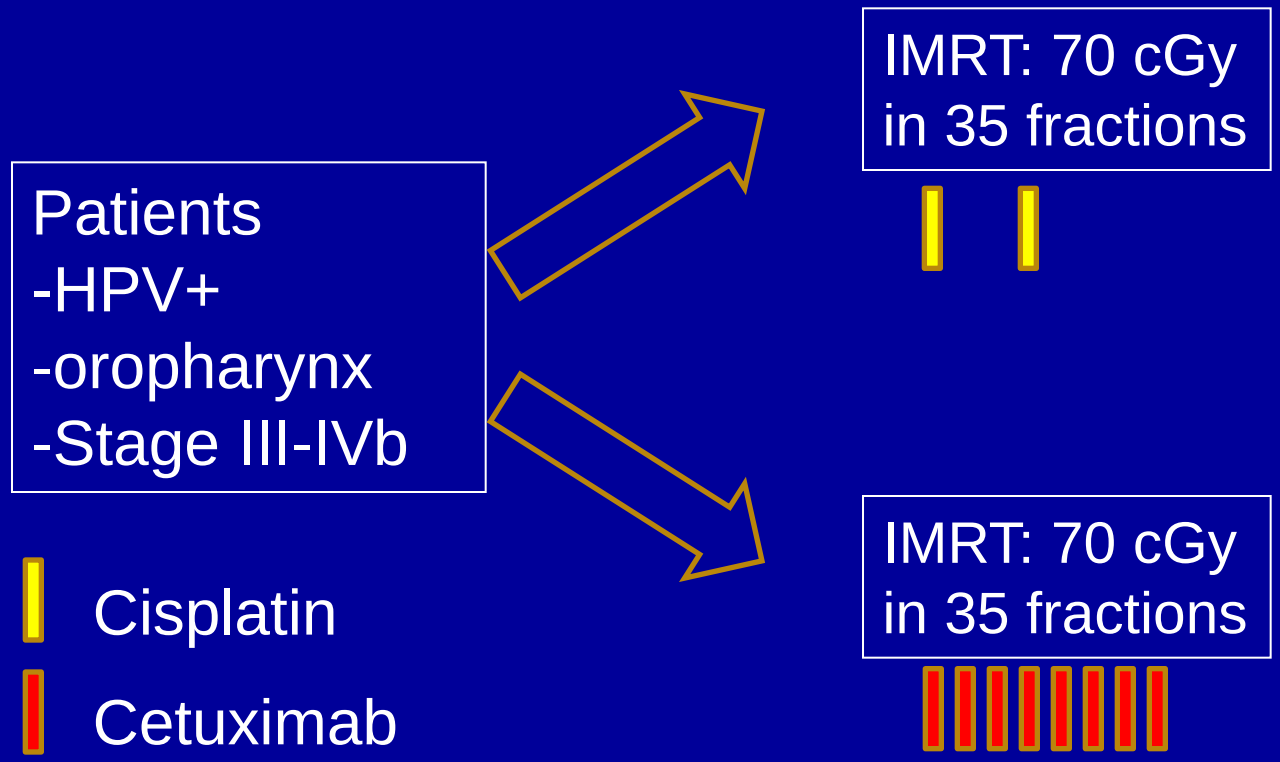
QUESTIONS ELICITED BY THIS STUDY

- The comparator arm did substantially better than probably expected:
  - DeCIDE ASCO 2012 Cohen et al
  - PARADIGM ASCO 2012 Haddad et al
  - CONCERT 1 ASCO 2012 Giralt et al
- This needs to prompt a careful design of future trials

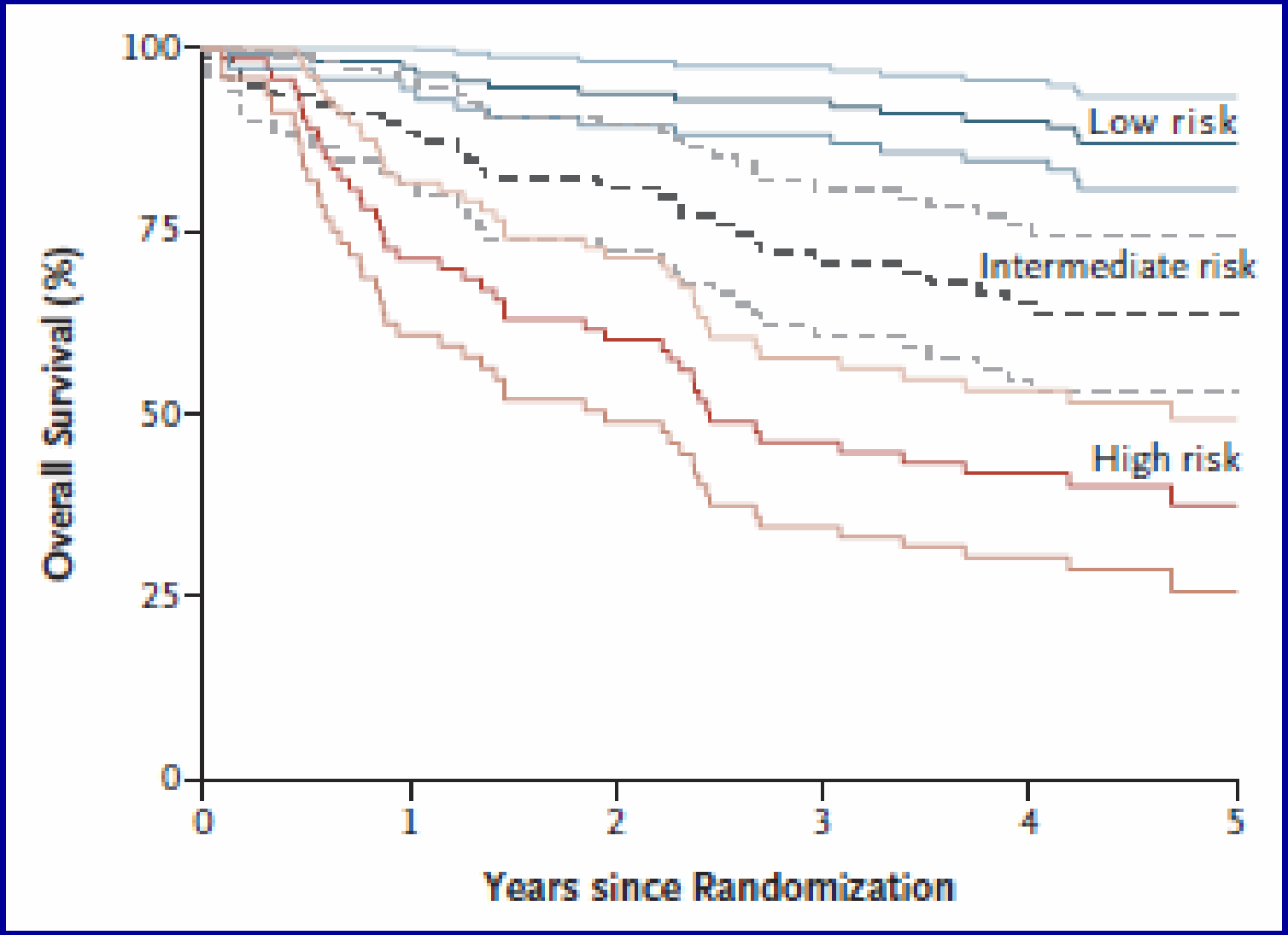
QUESTIONS ELICITED BY THIS STUDY

- Optimal sensitizing agent with current RT
  - CDDP vs cetuximab question not fully addressed.
- Influence of improved radiation in tolerability of CRT.
  - Lower age increases effectiveness of CRT with cisplatin per MACH-NC meta-analysis (in CONCERT-2 84% were <65).
- HPV context: 48% of patients were oropharyngeal HNSCC:
  - Better performance status?
  - Different biology?

RTOG 1016 is addressing the same question in HPV+



RTOG 0129: Overall Survival based on HPV-based Prognostic Stratification



93% at 3-yr

71%

46%

Ang, et al. NEJM 2010

DISCUSSION

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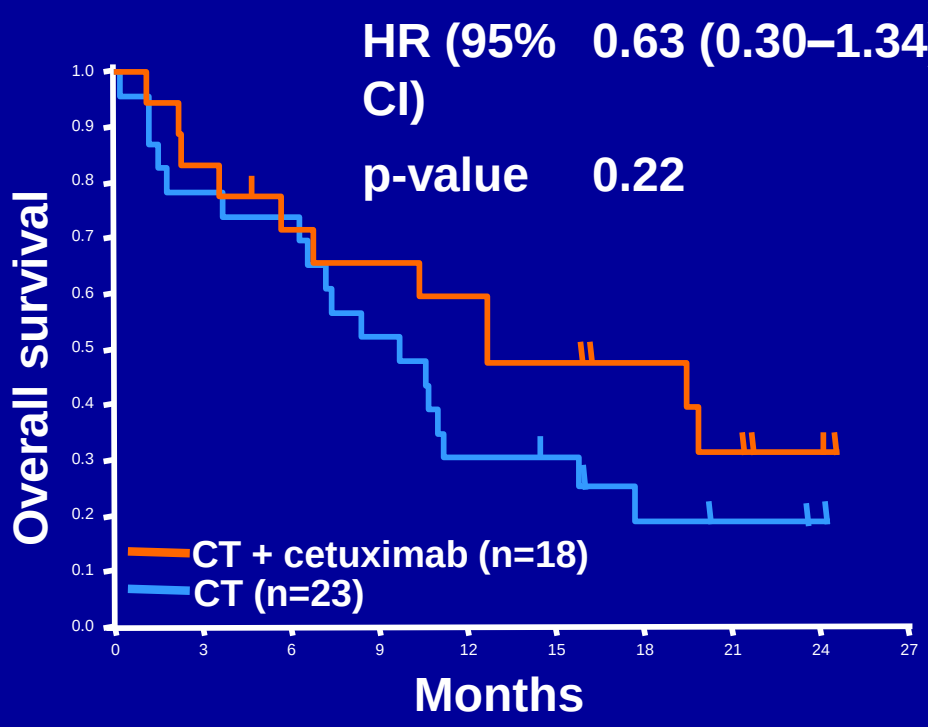
Overall Survival by p16 Status

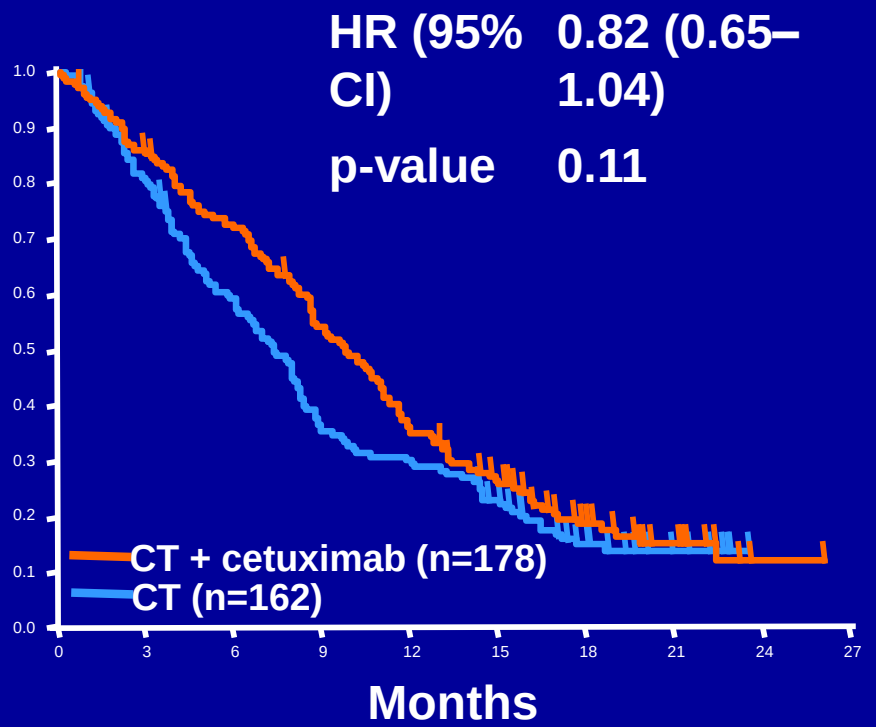
p16+ patients



Number of patients at risk

18	15	12	11	10	8	6	4	1	0
23	18	17	12	7	6	3	2	1	0

p16− patients



Number of patients at risk

178	150	126	93	61	40	19	10	1	0
162	128	92	56	47	33	15	6	0	0

HRs are CT + cetuximab vs CT.
CI, confidence interval; HR, hazard ratio.

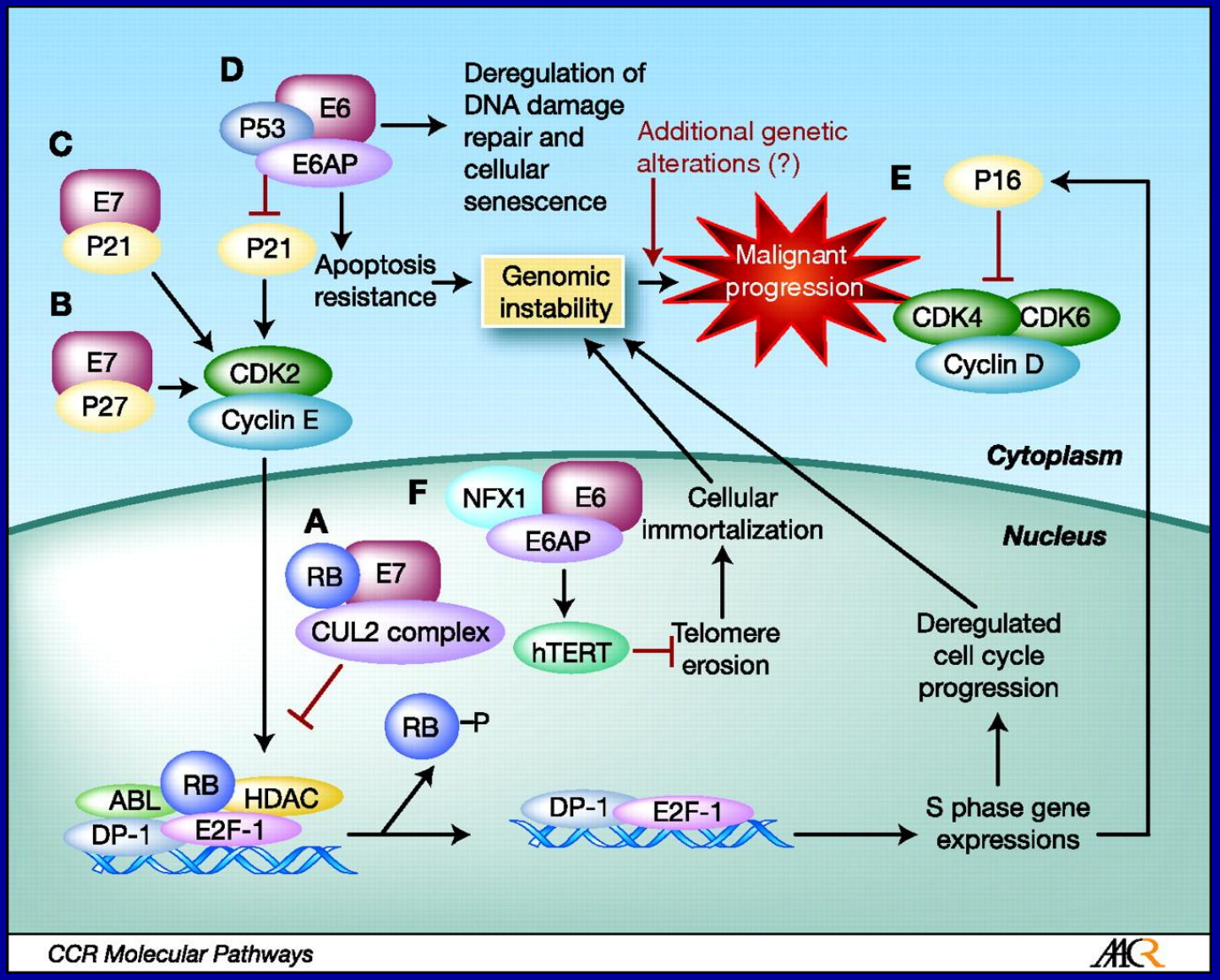
CONCLUSIONS

- The authors are to be commended for the thorough sample management:
  - Most (86%) patients were evaluable for p16 as a surrogate marker for HPV, with 9.2% having p16+ tumors.
- All subgroups were comparable regarding demographics and baseline characteristics.
- Patients, independent of tumor p16/HPV status, seemed to benefit from the addition of cetuximab to platinum-based chemotherapy, however with 9.2% rate of p16 positivity statistical power is limited.

QUESTIONS ELICITED BY THIS STUDY

- Do EGFR inhibitors have antitumor effect in HPV+ HNSCC?
  - Retrospective MSKCC series, Koutcher et al.
  - SPECTRUM, Vermorken et al.
  - Afatinib vs Cetuximab, Seiwert et al.

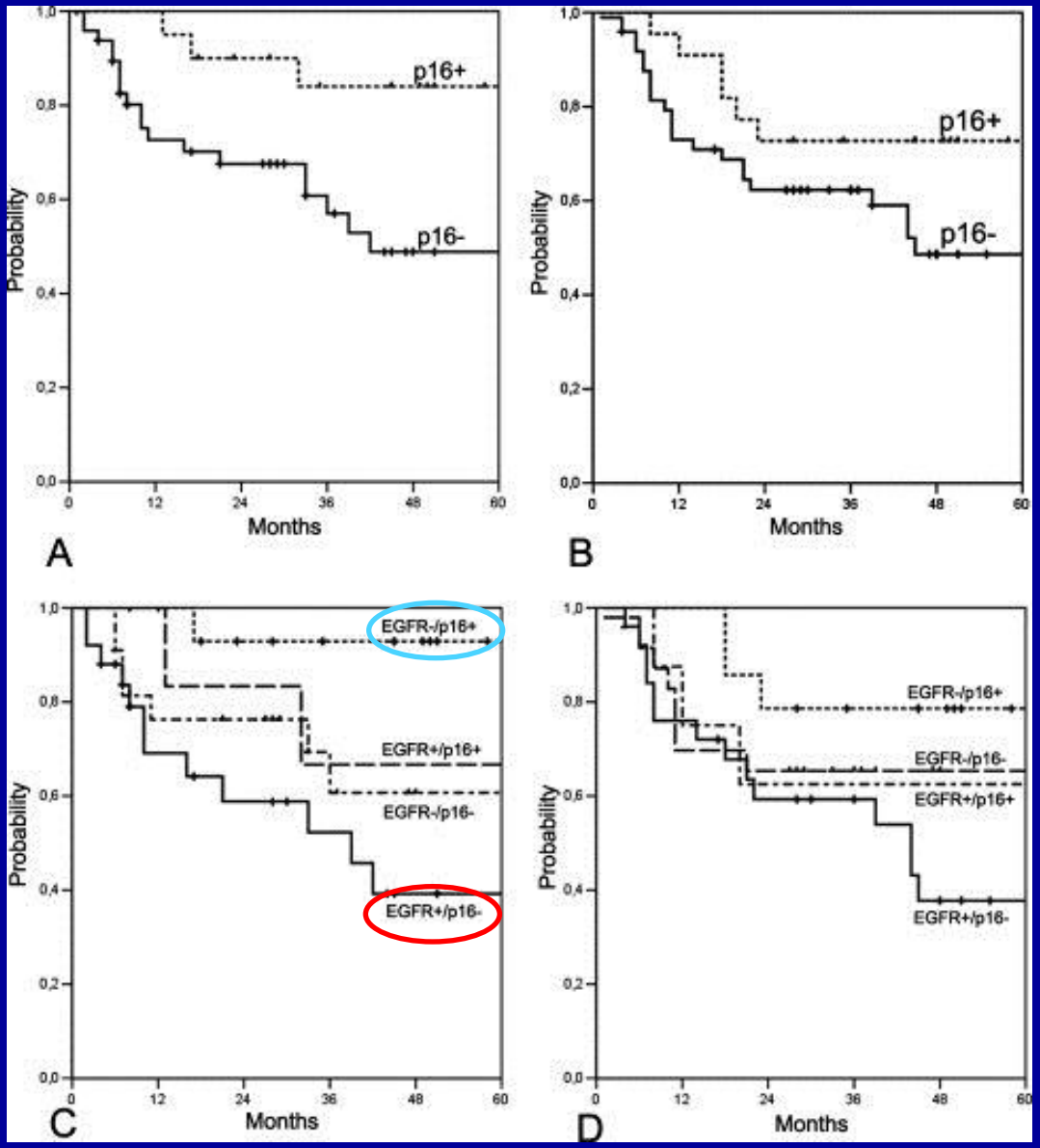
THE SCIENCE BEHIND: HPV oncogenic mechanism



Clin Cancer Res 2009; 15:6758

THE SCIENCE BEHIND

EGFR IHC expression differs in HPV+ vs HPV - HNSCC

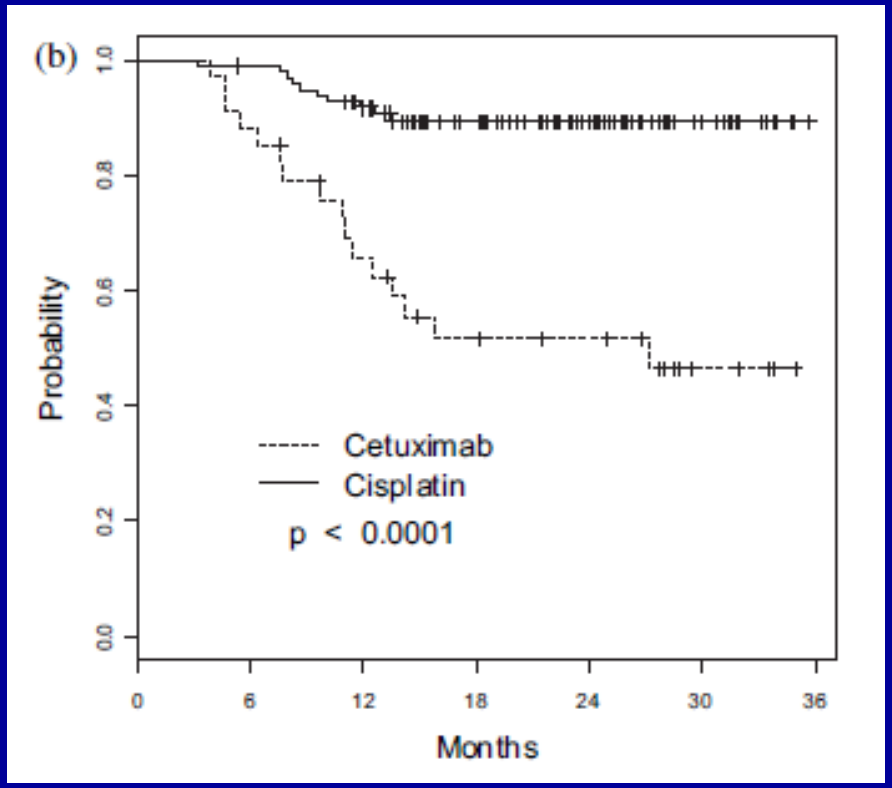


Int J Cancer. 2007;120:1731-8.

Cisplatin and RT versus cetuximab and RT in the context of human papillomavirus (HPV) and p16 in LAHNC

On multivariate analysis, with the inclusion of HPV and p16 data, treatment with CDDP/RT still predicted for improved LRC and DFS:

	CDDP Hazard ratio (95% CI)	C225 Hazard ratio
Locoregional control	0.14 (0.04 – 0.53)	1.00
Disease-free survival	0.18 (0.06 – 0.50)	1.00



Oropharynx

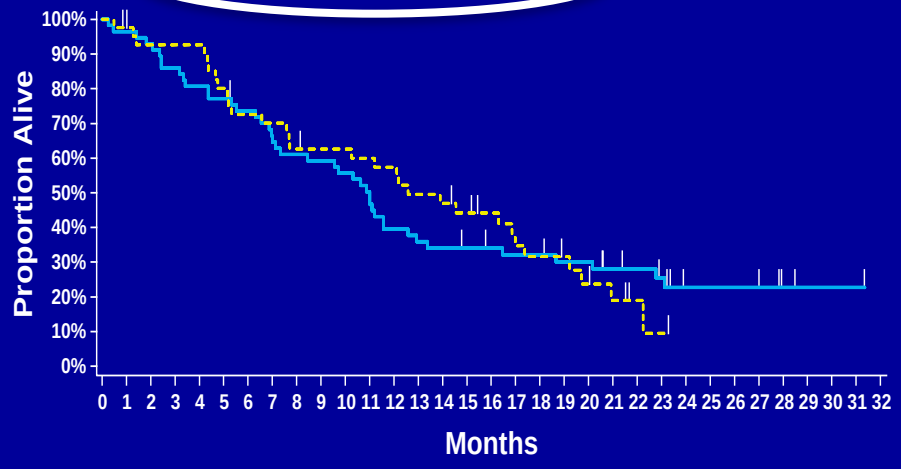
Koutcher et al, IJRBP

SPECTRUM : OS by HPV Status

HPV-Positive

HR = 1.00 (95%CI: 0.62 - 1.61)

p-value = 1.00



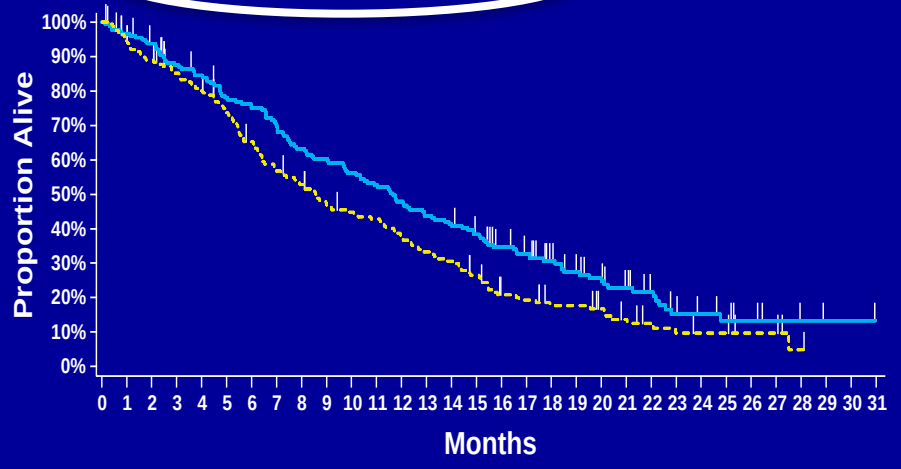
Subjects at risk:

Pmab + chemo	57	55	53	49	46	44	41	37	34	33	31	28	22	20	19	18	17	16	16	15	15	12	11	9	5	5	5	5	2	1	1	1	0
chemo alone	42	40	37	37	37	32	29	28	25	24	24	23	22	19	18	16	14	11	10	8	6	4	2	1	0	0	0	0	0	0	0	0	0

HPV-Negative

HR = 0.73 (95%CI: 0.58 - 0.93)

p-value = 0.01



Subjects at risk:

Pmab + chemo	179	171	164	150	144	132	127	119	107	102	95	89	81	74	70	63	53	48	39	32	28	22	17	11	9	7	5	3	2	1	1	0
chemo alone	165	154	144	134	126	114	100	87	80	71	66	63	56	49	45	38	27	25	20	20	16	12	9	7	6	6	4	4	1	0	0	0

	Median OS (95% CI) months
Pmab + CT (n = 57)	11.0 (7.3 - 12.9)
CT alone (n = 42)	12.6 (7.7 - 17.4)

	Median OS (95% CI) months
Pmab+ CT (n = 179)	11.7 (9.7 - 13.7)
CT alone (n = 165)	8.6 (6.9 - 11.1)

Quantitative interaction test p-value = 0.25

A randomized, open-label, Phase II study of afatinib (BIBW 2992) versus cetuximab in R/M HNSCC

Tanguy Seiwert, J. Fayette, J. M. Del Campo, P. Clement, R. Hitt, D. Cupissol, M. Degardin, W. Zhang, A. Blackman, E. Ehrnrooth, E. Cohen

	Afatinib	Cetuximab
Total randomized, n (%)	62 (100.0)	62 (100.0)
Disease control (CR, PR, SD), n (%)	**31 (50.0)**	**35 (56.5)**
95% CI	37.0%, 63.0%	43.3%, 69.0%
Objective response (CR, PR), n (%)	**10 (16.1)**	**4 (6.5)**
95% CI	8.0%, 27.7%	1.8%, 15.7%
Objective response (CR, PR), %	**19.2**	**7.3**
Partial response, n (%)	10 (16.1)	2 (3.2)
Stable disease, n (%)	21 (33.9)	31 (50.0)

	Afatinib response (%)	Cetuximab response (%)
p16		
Positive	1/9 (11.1)	0/8 (0.0)
Negative	5/25 (20.0)	2/23 (8.7)
EGFR vIII mutation		
Positive	0/0 (0.0)	0/0 (0.0)
Negative	6/25 (24.0)	2/28 (7.1)

Courtesy of Ezra Cohen

CONTEXT AND FUTURE

- Whereas in the EXTREME trial only 9.2% (of 381) of evaluable patients were p16/HPV+, in the SPECTRUM trial 22% (of 443) were HPV+.
- Slightly different chemotherapy backbone:
  - EXTREME: cisplatin 64% and carboplatin 36% (with 10% added during therapy)
  - SPECTRUM: cisplatin 100% initially
- Shifting population: EXTREME enrolled between 2004-2005 and SPECTRUM from 2007-2009.
- Do we need to investigate new targets for HPV-related HNSCC?

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CAPRA: Clinical trial design

Phase I dose escalation of 30-50 mg/week everolimus combined with AUC2 carboplatin and 60 mg/m2 paclitaxel weekly

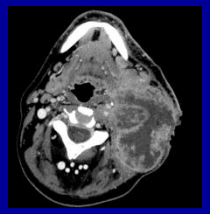
No DLT

Phase II evaluation (two stage Simon design)

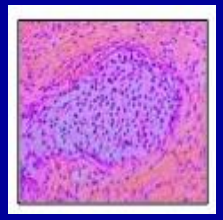
- Everolimus (RD)
- Carboplatin AUC 2
- Paclitaxel 60 mg/m²

Each week

Chemoradiation therapy

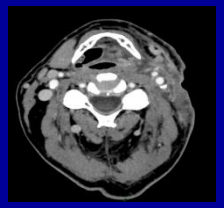


Baseline CT-scan

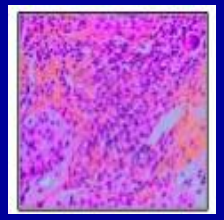


Pretreatment Biopsy

Weekly cycles x 9

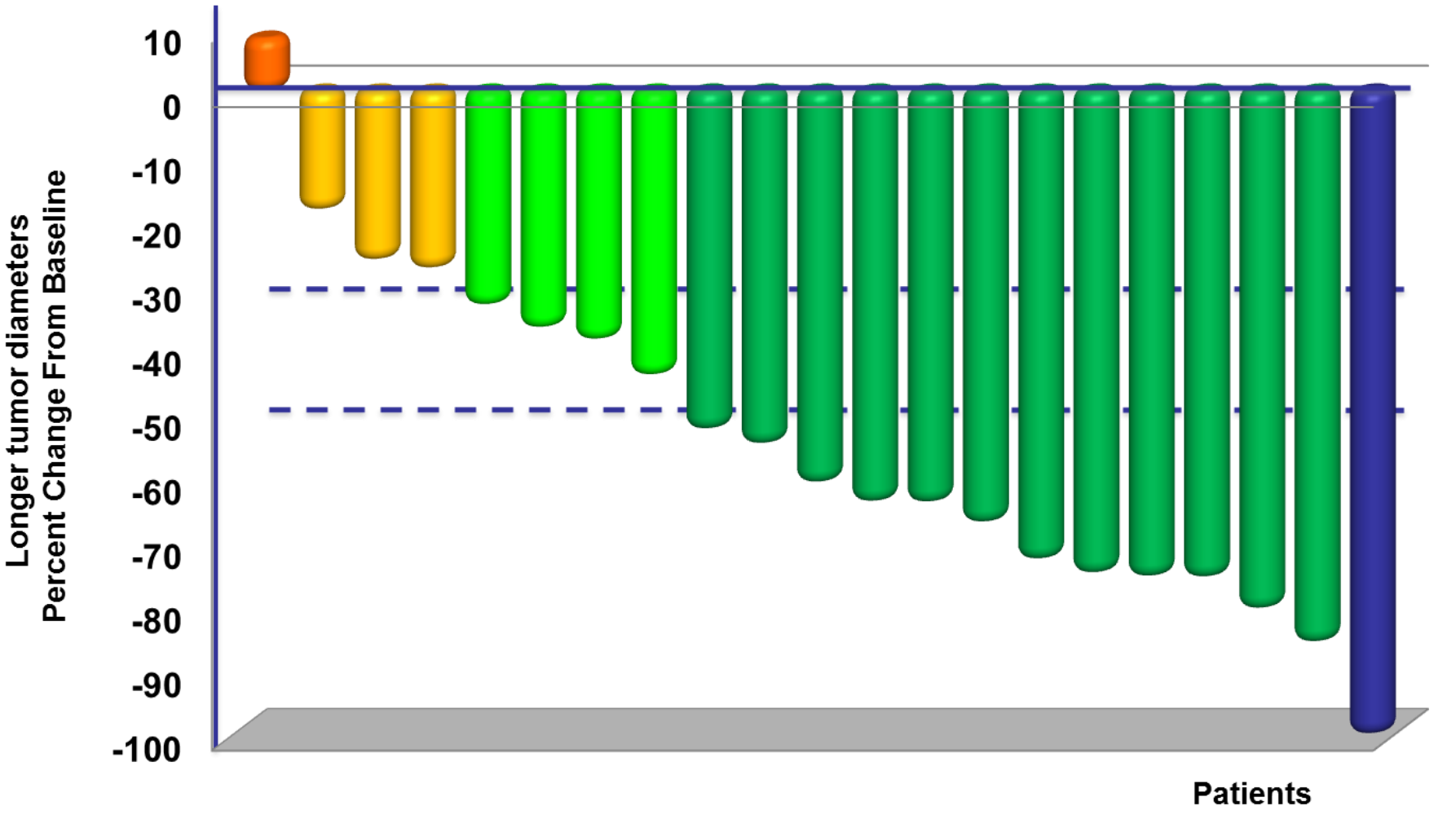


Post-treatment CT-scan



Post-treatment Biopsy

Waterfall plot evaluation of patients treated with CAPRA (RECIST1.1)

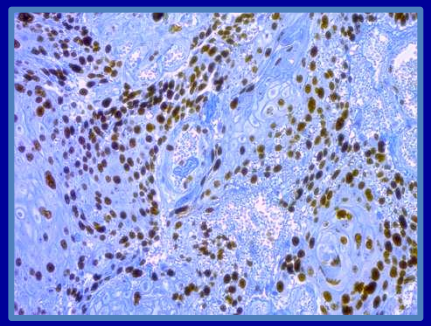


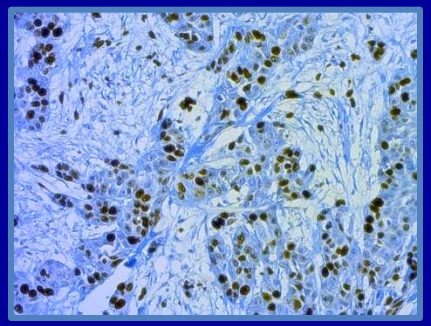
Pre- & Post-Treatment Biomarkers

Baseline Post-CAPRA

Ki67

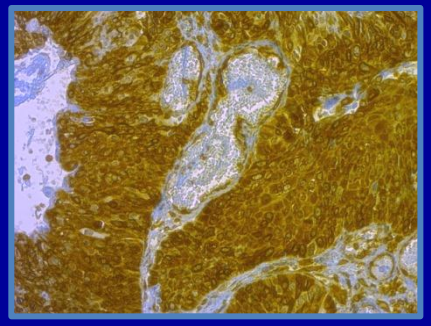
IHC

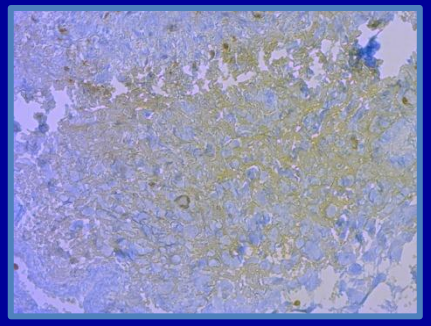




p-S6K

IHC





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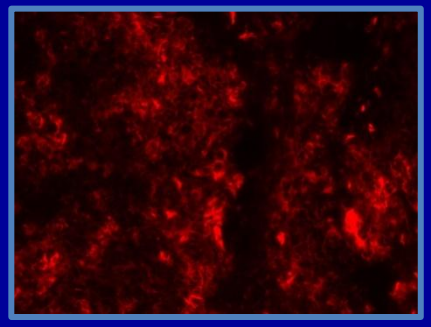
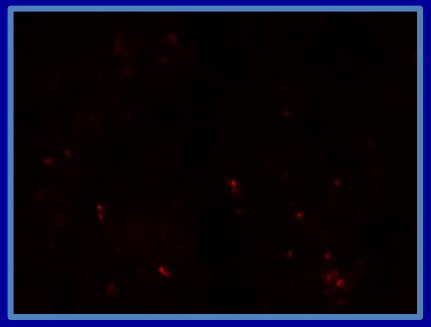
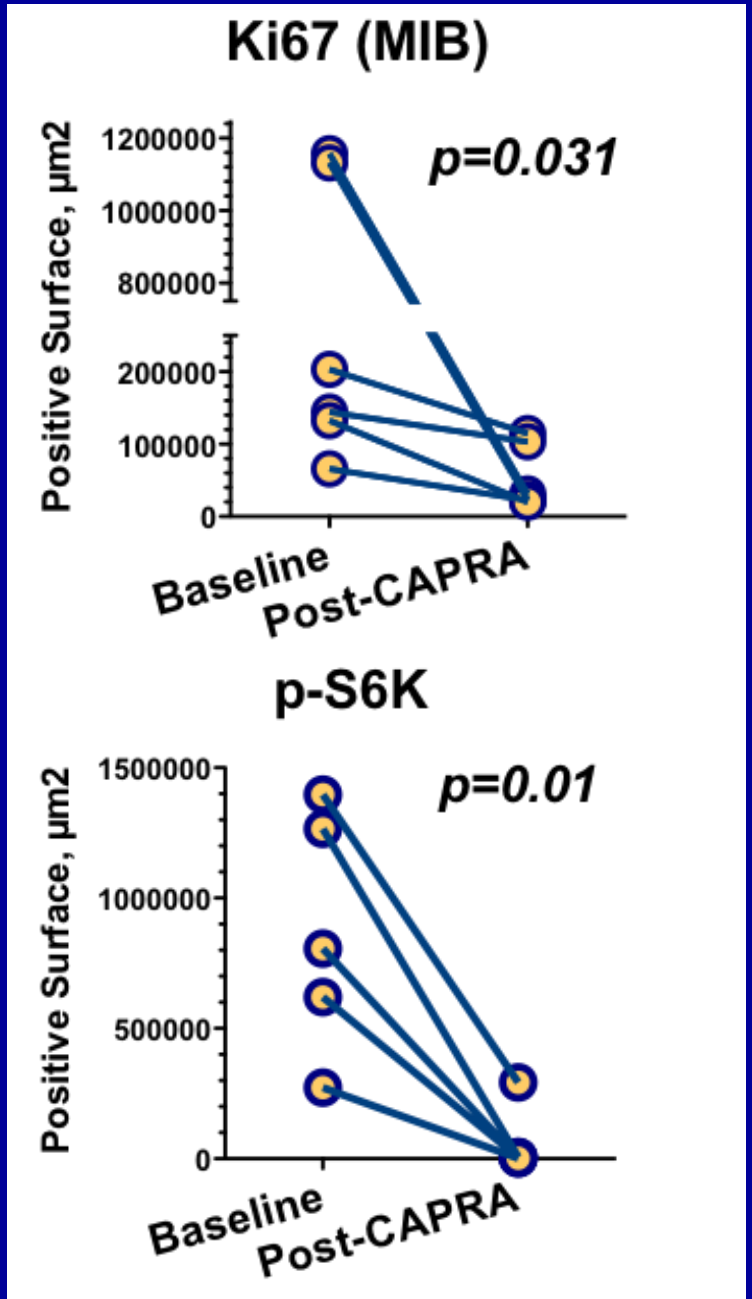






CONCLUSIONS

- The authors are to be commended for navigating through the hazards of a sequential biopsy study to help us all understand the molecular events after targeted therapy.
- Everolimus plus carboplatin and paclitaxel is well tolerated as is effective in patients with locally advanced HNSCC.
- Translational studies in tumor indicate that everolimus significantly affects mTOR functions in patients treated with CAPRA.

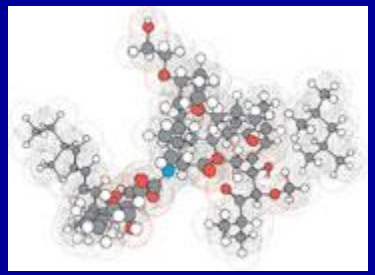
QUESTIONS ELICITED BY THIS STUDY

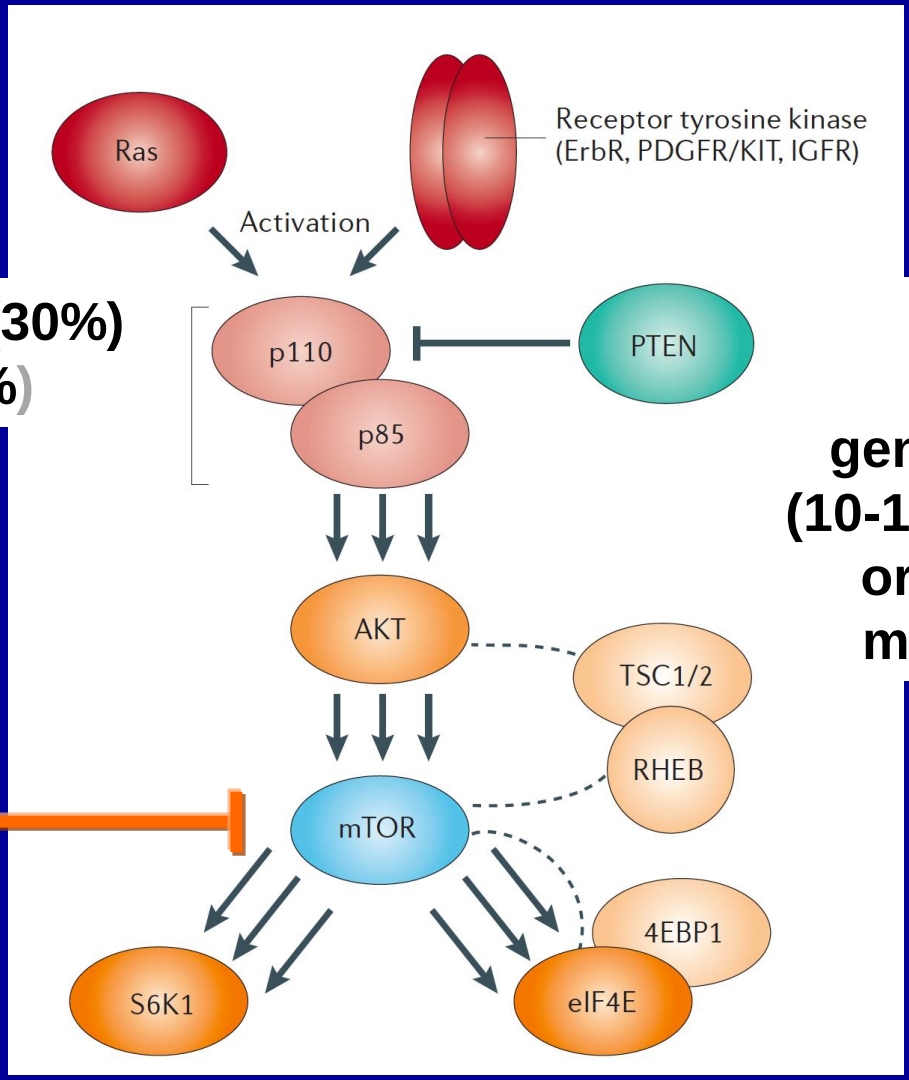
- What is the role of the PI3K/Akt/mTOR pathway in HNSCC?
- Do such pathway inhibitors have antitumor effect in HNSCC?

THE SCIENCE BEHIND

PIK3CA amplification (30%) or mutation (6-11%)

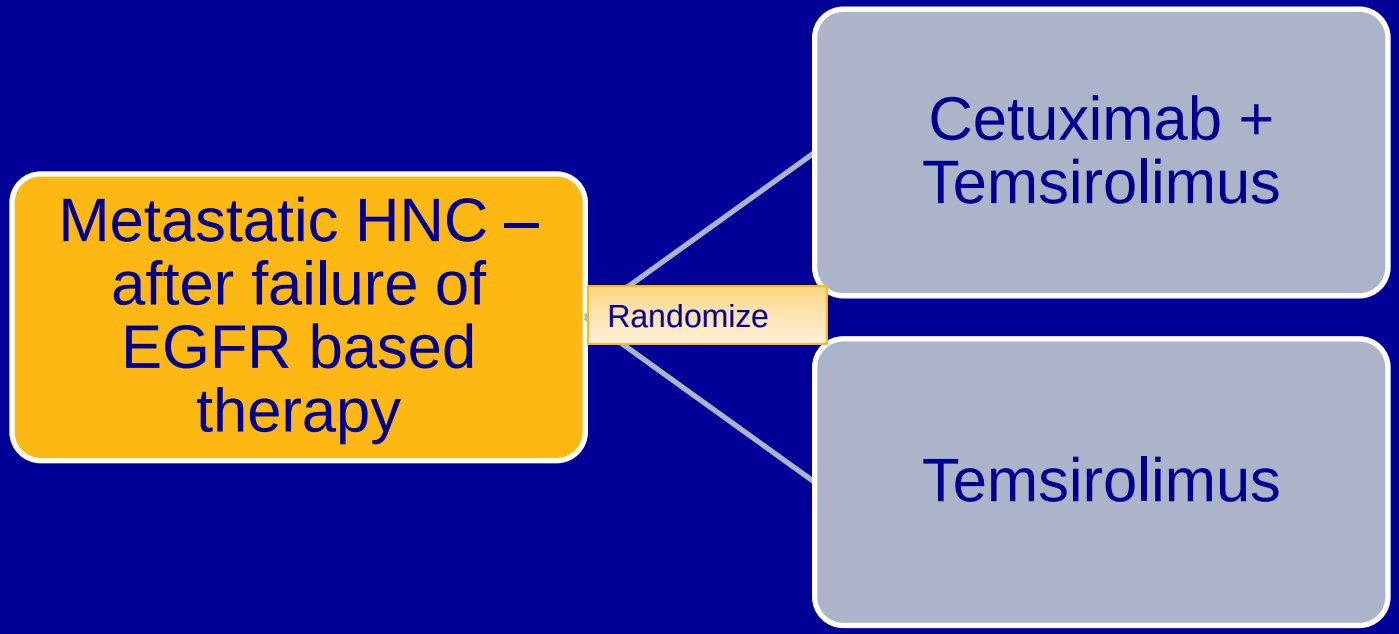
Everolimus





gene mutation (10-15%), deletion or promoter methylation

Multicenter randomized Phase II Trial of combined EGFR/mTOR inhibition *(PIs: T. Seiwert, R. Xing, Y. Lussier)*



N = 80 (40 each group)

CT Scans every 2 months

Primary outcome: Progression free

Courtesy of Ezra Cohen

THE SCIENCE BEHIND: PIK3CA as a target

- 12 canonical mutations detected in 120 HNC tumor samples (E545K, H1047R, E545Q, M1043I)
  → 10% incidence

- 11 canonical PIK3CA mutation in 55 HPV(+) HNC
  → **20%** incidence

- HPV(-) HNC harbors atypical PIK3CA mutations/SNPs, but very few canonical mutations

- PIK3CA copy number is increased in **29%** of HNSCC -- both HPV(+) and HPV(-) (N=26/89, mostly low level CN increases)

Seiwert, ASCO 2012 -- Courtesy of Ezra Cohen